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Cardiovascular risk assessment with pulse wave velocity, intima media thickness, and flow-mediated dilatation in patients with idiopathic pulmonary fibrosis

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ABSTRACT

Aim: The underlying mechanism of fibrotic lung diseases predisposing to coronary artery disease is not yet clear. Chronic inflammation may contribute to atherosclerosis and play a role in increased cardiovascular risk. To study investigate subclinical atherosclerosis by measuring carotid femoral pulse wave velocity (PWV), carotid intima media thickness (CIMT), and flow-mediated dilatation (FMD) in patients with idiopathic pulmonary fibrosis (IPF).

Material and Method: This cross-sectional study consisted of 55 newly diagnosed IPF patients and 55 healthy controls between September 2019 and September 2021. Cardiovascular Risk Assessment was evaluated by endothelial function measured by FMD, CIMT measured by carotid doppler ultrasonography, and arterial stiffness measured by PWV.

Results: In multivariable regression models, the presence of IPF was common independent predictor of CIMT (β±SE=0.18±0.05, p=0.002), log(FMD) (β±SE=−0.15±0.04, p<0.001) and log(PWD) (β±SE=0.16±0.03, p<0.001). An increase log(PWV) levels were common independent predictors of CIMT and log(FMD). The levels of CRP were positively correlated with CIMT (r=0.359, p=0.009) and PWV (r=0.338, p=0.018) levels, while it was negatively correlated with FMD levels (r=-0.372, p=0.004).

Conclusions: IPF patients have elevated risk of endothelial dysfunction and atherosclerosis. A sustained inflammatory response may have play an important role in the process of atherosclerosis.

Keywords: Cardiovascular disease, coronary artery disease, pulmonary fibrosis, atherosclerosis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease of unknown etiology that is associated with significant morbidity and mortality, and characterized by an abnormal accumulation of fibrotic tissue in the lung parenchyma (1). IPF may present with nonspecific symptoms, such as dyspnea, cough, and low exercise capacity. Many of these symptoms can be similar to those of heart failure, and therefore, it requires a multidisciplinary approach (2). Recent epidemiological evidence has suggested that patients with IPF are at increased risk of cardiovascular disease (CVD) (3, 4). The mechanisms between IPF and CVD are still unclear. However, chronic inflammatory processes may contribute to the formation of atherosclerosis.

Atherosclerosis is a complex inflammatory-fibroproliferative response that develops against the accumulation of atherogenic lipoprotein originating from the blood plasma in the arterial intima (5). The carotid intima-media thickness (CIMT) test is a simple and inexpensive technique to evaluate the cumulative effect of atherosclerotic risk factors (6). However, endothelial dysfunction is observed in the early phase of atherosclerosis (7). Endothelial dysfunction refers to impaired nitric oxide (NO) production and/or an imbalance in relaxation and contraction factors, such as endothelium-derived endothelin1 (ET-1), angiotensin, and oxidants. Flow-mediated dilation (FMD) is a good ultrasonographic

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marker of early atherosclerotic changes that is used to measure endothelial function, as it demonstrates the vasodilation response of peripheral arteries to physical stimuli. Endothelial dysfunction is a well-known response to cardiovascular risk factors (8).

Previous studies have suggested that fibrotic lung disorders predispose to coronary artery disease (CAD) (9,10). To the best of our knowledge, in the literature, we did not identify a study in which subclinical atherosclerosis was detail evaluated by cardiovascular risk tests in IPF patients. Therefore, in the present study, we aimed to investigate cardiovascular risk assessment by FMD, CIMT and pulse wave velocity (PWV), which marker for subclinical atherosclerosis, in patients with IPF compared to and age and sex and smoking matched healthy controls.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Training and Research Hospital Ethics Committee (Date: 13.09.2019, Decision No: 1985). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This research was conducted as a cross sectional study between September 2019 and September 2021. Written informed consent was obtained from all of the participants.

Fifty-five consecutive patients with newly diagnosed IPF, who were over 18 years of age, in the Department of Chest Diseases and referred for evaluation of cardiac symptoms were included in the study. The diagnosis of IPF was made according to the 2018 international IPF guideline (1). All patients had pathological usual interstitial pneumonia or patern on chest high resolution computed tomography. While selecting the healthy control group, we evaluated the patients presenting with general examination (ICD code: Z00.8) between September 2019 and September 2020. We identified 460 patients without any health problems in the 12-month period. Afterwards, 1:1 matching method was performed between the control group and IPF patients in terms of age and sex and smoking.

Patients with a history of coronary artery disease, pulmonary arterial hypertension, kidney disease (defined as patients with an estimated glomerular filtration rate (eGFR) of<15 ml/min/1.73 m2, or who require hemodialysis or peritoneal dialysis treatment), liver diseases (including active hepatitis and liver cirrhosis), documented sleep apnea, thyroid diseases, asthma, malignancy, any inflammatory diseases were excluded from the study.

Demographic, laboratory and clinical findings were recorded in patient files at the time of admission to the hospital.

Biochemical Parameters

Venous blood samples were taken in first admission, and analyzed for a complete blood count and lipid and cardiac biomarkers. Collected blood samples were centrifuged at 1500 rpm for 10 minutes to measure the determined parameters. Triglycerides and total cholesterol were measured using the enzymatic colorimetric method, high-density lipoprotein (HDL) cholesterol was measured using the homogeneous enzymatic colorimetric method, and albumin was measured using the brom cresol green method on a Beckman Coulter AU681-10 autoanalyzer (Danaher Corp., CA, USA). Low-density lipoprotein (LDL) was measured using the Friedewald formula. Thrombocytes were measured using the impedance (resistance) method, and the other hematological parameters were measured using the Sysmex XE 2100 hematology analyzer (Roche Diagnostic Corp., IN, USA). Hemoglobin was measured photometrically. Kidney function test were measured by colorimetric method (Cobas 8000, Roche, Germany), C – reactive protein (CRP) was measured turbidimetric method on a Beckman Coulter AU 5800 autoanalyzer (Danaher Corp., CA, USA).

Echocardiography

Echocardiography procedures were performed using a Philips Affiniti 70G Ultrasound 2.5-MHz transducer echocardiography device (Koninklijke Philips N.V., Eindhoven, Netherlands) by a cardiologist who had no knowledge about the study. Parasternal long- and short-axis views, and apical 2- and 4-chamber views were obtained. The left ventricular diameters were measured from the M-mode images in parasternal long axis view. The modified Simpson method was used to calculate the left ventricle ejection fraction using the apical 4-chamber views. Tricuspid regurgitation was accepted as jet area 5 cm2 and above.

Carotid Doppler Ultrasonography

The CIMT was measured with the patient in the supine position with both hands under his or her head. The measurements were performed using a GE LOGIQ S8 high-resolution B-mode ultrasound device (Gyeonggi-do, Korea) by a radiologist who had no knowledge about the clinical statuses of the patients.

In these measurements, the right and left main carotid arteries were evaluated with an automated system using a linear probe. The measurements were performed from 3 points: right and left main carotid arteries, bifurcation, and first 2-cm part of internal carotid arteries. Longitudinal measurements were performed from the distances defined between the vascular lumen echogenicity and media adventitia echogenicity. The CIMT was calculated by taking the average of the 3 measurements made for both carotid arteries.

Flow-Mediated Dilation

The FMD technique was used to evaluate the endothelial functions in the brachial artery. The patients were placed in a comfortable position on their backs. A 10-Mhz transducer was placed on the right brachial artery trace at 4–5 cm above the elbow, and was imaged longitudinally along the arterial trace, where the best image was obtained. The projection of the edge of the transducer was marked on the skin using a pencil by keeping the transducer fixed where the appropriate image was obtained. The brachial artery diameter (intima-to-intima) was measured 3 times and the average of these 3 measurements was recorded as the basal diameter. These measurements taken from the brachial artery were taken at the end of the diastole according to the ECG trace. After the basal brachial artery diameter was recorded, the cuff of the sphygmomanometer was tied to the arm. It was inflated at an average pressure of 200 mmHg and kept in this way for 5 min. The cuff was then abruptly lowered and the transducer was properly placed on the skin at the point that had been previously marked using a pencil. In order to evaluate the hyperemic response, the brachial artery image was taken for 90 second and the artery diameter at first minute was measured at the end of diastole. The percentage change in the FMD value with respect to the basal vessel diameter was calculated according to the formula below.

FMD%=[(peak diameter–baseline diameter)/ baseline diameter]×100

Pulse Wave Velocity

The pulse wave velocity (PWV) was calculated using the SphygmoCor system (AtCor Medical, West Ryde, NSW, Australia). Patients were monitored primarily with 3-channel ECG. Then, after resting for 10 minutes in the supine position, the ultrasound probe was placed in the left supraclavicular fossa and angulated medially to target the subclavian artery exit from the aorta, and the right femoral artery was used as the distal measurement point. In the Doppler spectral recording taken from the aorta and femoral artery using a continuous-wave doppler, the systolic deflection starts were taken as the reference point and the distance differences between the R wave on the ECG recordings were recorded as the time between the reference points [transit time (T)] of the PWV. Next, the distance between the reference points (D) was determined in meters with the surface measurement. Accordingly, it was calculated as PWV=D/T (m/s).

Statistical Analysis

Normality testing was performed with the Kolmogorov-Smirnov test. Normal distributions were shown as mean±standard deviation and non-normal distributions as median (interquartile range (IQR): 25–75). Categorical variables were expressed as numbers and percentages. Differences between groups of numerical variables were evaluated with Student T-test or Mann-Whitney U test according to normality distribution. Comparison of categorical variables were performed Chi-square, Yates correction, and Fisher exact tests. The correlation between numerical variables were tested by Pearson and Spearman correlation analysis. Stepwise multivariable linear regression analyses were conducted to establish any possible independent predictors of CIMT, FMD and PWV. All statistical data were analyzed by STATA (StataCorp, Texas, ABD), and $p<0.05$ was considered to be statistically significant.

RESULTS

The IPF group consisted of 40 male (72.7%) and 15 female (27.3%) patients (mean age 65.0±9.8 years). The mean age, gender distribution and smoking rate were similar between the IPF group and the control group. The demographic and clinical findings are shown in detail in **Table 1**. The mean CIMT (1.1±0.4 mm vs. 0.8±0.2 mm; p=0.002), median PWV (16.4 vs. 11.4 m/s, p<0.006), mean leukocyte (9.6±2.2 vs. 7.2±2.1 ×103/μL, p<0.001), mean HCT (42.6±4.8 vs. 39.8±3.2 %, p=0.002), and median CRP (5.4 vs. 2.7 mg/L, p<0.001) levels were higher in IPF group compared to the control group, and median FMD was lower (8.7 vs. 14.7 %, p=0.010) (**Table 1**).

There was a positive correlation between the CIMT and PWV levels (r=0.536, p<0.001). There was negative correlation between FMD and CIMT (r=–0.544, p<0.001) and PWV levels (r=–0.419, p<0.001). The CRP levels were positively correlated with CIMT (r=0.359, p=0.009) and PWV (r=0.338, p=0.018) levels, while it was negatively correlated with FMD levels (r=-0.372, p=0.004) (**Table 2**).

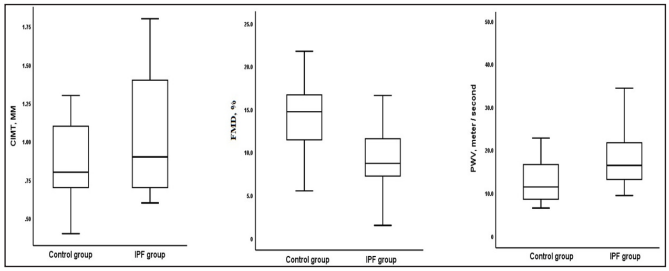

Figure 1. Cardiovascular risk indicators in IPF patients

Abbreviations: IPF: Idiopathic pulmonary fibrosis, PWV: Pulse wave velocity, FMD: Flow-mediated dilation, CIMT: Carotid-intima media thickness.

Table 1. Distribution of the demographic and clinical findings in study population.

Variables	Control group	IPF group	p
	n=55	n=55	
Demographic findings			
Age, years	63.6±9.5	65.0±9.8	0.449
Gender, n(%)			0.536
Male	36 (65.5)	40 (72.7)	
Female	19 (34.5)	15 (27.3)	
BMI, kg/m²	23.8±2.6	24.6±3.5	0.176
Smoke, n(%)	14 (25.5)	16 (29.1)	0.831
Diabetes mellitus, n(%)	-	11 (20.0)	-
Hypertension, n(%)	-	18 (32.7)	-
Gastroesophageal reflux, n(%)	-	15 (27.3)	-
SBP, mm Hg	118.1±12.6	122.3±11.8	0.074
DBP, mm Hg	70.1±8.6	72.8±11.3	0.161
Drugs, n(%)			
Drug-free or steroid	-	10 (18.2)	-
Pirfenidon	-	32 (58.2)	
Nintedanib	-	13 (23.6)	
Echocardiographic findings			
EF, %	59.5±2.4	58.6±3.2	0.149
Tricuspid regurgitation, n(%)	3 (5.5)	5 (9.3)	0.716
PAB, mmHg	27.8±6.8	32.7±11.3	0.055
Laboratory findings			
Hemoglobin, g/dL	13.6±1.1	13.9±1.7	0.267
Leukocyte, ×10³/μL	7.2±2.1	9.6±2.2	<0.001
Platelet, ×10³/μL	229.5±51.6	251.1±63.8	0.053
HCT, %	39.8±3.2	42.6±5.6	0.002
Triglycerid, mg/dL	147 (97-184)	123 (97-152)	0.202
HDL, mg/dL	50.1±11.2	49.4±15.8	0.797
LDL, mg/dL	138 (97-163)	132 (103-151)	0.722
Albumin, g/dL	42.1±7.7	41.2±3.3	0.424
UREA, mg/dL	32 (26-45)	33 (27-40)	0.914
Creatinine, mg/dL	0.8±0.2	0.9±0.4	0.124
Sodium, mmol/L	140.6±2.4	136.5±19	0.113
Potassium, mmol/L	4.4±0.3	4.5±0.4	0.362
CRP, mg/L	2.7 (0.9-5.6)	5.4 (2.9-13.3)	<0.001
Vascular parameters			
CIMT, mm	0.8±0.2	1.1±0.4	0.002
FMD, %	14.7 (11.4-16.7)	8.7 (7.1-11.9)	0.010
PWV, meter / second	11.4 (8.4-16.6)	16.4 (13-21.9)	<0.001

Categorical variables are expressed as the number (%), while numerical variables are expressed as the mean±standard deviation or median (IQR: 25–75).
Abbreviations: EF: Ejection fraction, PAB: Pulmonary artery pressure, CIMT: Carotid-intima media thickness, FMD: Flow-mediated dilation, PWV: Pulse wave velocity, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HCT: Hematocrit, CRP: C-reactive protein.

Table 2. Parameters associated with the CIMT, FMD and PWV levels.

Variables	CIMT		FMD		PWV	
	r	p	r	p	r	p
CIMT	-	-	-0.544	<0.001	0.536	<0.001
FMD	-0.544	<0.001	-	-	-0.419	<0.001
Age	0.436	<0.001	-0.308	0.013	0.291	0.020
BMI	0.218	0.096	0.182	0.090	0.136	0.164
EF	-0.137	0.154	0.114	0.236	-0.053	0.581
PAB	0.179	0.101	-0.154	0.164	0.147	0.157
Hemoglobin	-0.118	0.222	-0.012	0.899	0.081	0.404
Leukocyte	0.281	0.048	-0.361	0.006	0.313	0.025
Platelet	0.131	0.174	-0.180	0.060	0.063	0.513
HCT	0.020	0.833	-0.129	0.179	0.152	0.126
Triglycerid	-0.131	0.171	-0.020	0.834	0.046	0.632
HDL	-0.319	0.016	0.310	0.013	-0.312	0.035
LDL	-0.149	0.191	-0.065	0.500	-0.045	0.644
Albumin	-0.111	0.250	0.184	0.084	-0.255	0.007
UREA	0.188	0.129	-0.065	0.502	0.075	0.439
Creatinine	0.133	0.160	-0.111	0.247	0.176	0.096
Sodium	0.012	0.904	0.120	0.201	-0.165	0.106
Potassium	0.155	0.146	-0.112	0.246	-0.098	0.469
CRP	0.359	0.009	-0.372	0.004	0.338	0.018

Abbreviations: EF: Ejection fraction, PAB: Pulmonary artery pressure, CIMT: Carotid-intima media thickness, FMD: Flow-mediated dilation, PWV: Pulse wave velocity, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HCT: Hematocrit, CRP: C-reactive protein.

In multivarible regression models, the presence of IPF was common independent predictor of CIMT (β±SE=0.18±0.05, p=0.002), log(FMD) (β±SE=–0.15±0.04, p<0.001) and log(PWD) (β±SE=0.16±0.03, p<0.001). Also, increasing log(PWV) values were common independent predictors of CIMT and log(FMD) (**Table 3**).

DISCUSSION

In this cross-sectional study was showed that subclinical atherosclerosis is increased in IPF patients without cardiovascular risk factors. The relationship between cardiovascular risk indicators and CRP levels supports that the inflammatory process may play a pathological role in atherosclerosis. In addition, PWV was found to be a common independent predictor of both CIMT and FMD.

Although the fibrotic process is limited to the lungs in IPF, cardiovascular comorbidities are frequently observed (11). Despite this frequency, the relationship has not yet been clarified. One of the prominent hypotheses is that IPF promotes atherosclerosis (12). Decreased lung function in patients with IPF can cause chronic hypoxemia, and the imbalance between oxygen demand and supply in the arterial wall may play a key role in the development of atherosclerotic lesions (13). In the process of atherosclerosis, specific conditions (anoxia, inflammation, oxidative stress) induce angiogenic factors and predispose the patient to

the formation of atherosclerotic plaques (14). Abundant angiogenic chemokine has been detected in tissue samples from animal models and patients with IPF (15). Cytokines of interleukin (IL)-4, tumor necrosis factor-α, and IL-13, which show high levels in pulmonary fibrosis patients, can lead to atherogenesis in various ways (16). A circulating angiogenic factor may arise from the systemic vascular endothelium and affect the lungs (15, 17).

Data collected from the TOMORROW and INPULSIS studies confirmed a history of atherosclerotic CVD in approximately 20% of IPF patients (18). In the literature, subclinical atherosclerosis in IPF patients had mostly studied with a single cardiovascular risk indicator. Consistent with previous studies, we showed that an increase CIMT and a decrease FMD levels in IPF patients (19, 20). Abnormal endothelial physiology plays a role in the early stage and formation of atherosclerosis as well as in dynamic plaque control in the late stage. This suggests that the increase in CIMT may be after the deterioration of endothelial function in the arterial vessel wall (21). On the other hand, the presence of IPF was an independent predictor for increased indicators of cardiovascular risk. This finding suggested that IPF may cause endothelial dysfunction and result in CVD by accelerating the atherosclerosis process. There are several mechanisms that support this hypothesis. Firstly, strong nitric oxide expression was observed in the macrophages, neutrophils, and alveolar epithelium in the lungs of the patients with IPF, and increased nitric oxide production is responsible for oxidative damage (22). Secondly, increased oxidative damage plays a role in the development of endothelial dysfunction (23). Thirdly, activation of inflammatory cells may contribute, or trigger, to atherosclerosis (24). In atherosclerosis, lipid accumulation and activation of inflammatory cells in the arterial intima play an important role (25). When tissue damage occurs, macrophages accumulate in the damaged tissue due to the inflammatory response, and CRP expression is induced and increases with the progression of atherosclerosis (26). A previous study demonstrated that a positive correlation between CRP and carotid plaque in IPF patients (19). This may explain that the association between cardiovascular risk indicators and high CRP and low HDL.

Table 3. Independent predictors of CIMT, FMD, and PWV levels.

Variables	Univariable Regression			Multivariable Regression		
	β±SE	95% CI lower; upper	p	β±SE	95% CI lower; upper	p
CIMT						
Age	0.02±0.01	0.01; 0.02	<0.001	0.09±0.02	0.05; 0.14	<0.001
Male gender	0.11±0.07	-0.30; 0.24	0.123	-	-	-
IPF presence	0.21±0.06	0.09; 0.33	0.001	0.18±0.05	0.07; 0.28	0.002
Leukocyte	0.08±0.01	-0.02; 0.03	0.529	-	-	-
HDL	-0.06±0.02	-0.10; -0.01	0.016	-	-	-
CRP	0.12±0.06	0.01; 0.24	0.011	-	-	-
log(PWV)	1.05±0.13	0.78; 1.31	<0.001	0.83±0.13	0.57; 1.09	<0.001
log(FMD)	-0.84±0.14	-1.11; -0.58	<0.001	-0.55±0.12	-0.81; -0.31	<0.001
				Adjusted R2= 0.568; p<0.001		
log(FMD)						
Age	-0.05±0.01	-0.09; -0.02	0.005	-0.04±0.02	-0.07; -0.01	0.030
Male gender	0.07±0.04	-0.08; 0.09	0.863	-	-	-
IPF presence	-0.19±0.03	-0.26; -0.13	<0.001	-0.15±0.04	-0.23; -0.08	<0.001
Leukocyte	-0.02±0.01	-0.03; -0.02	0.026	-	-	-
HDL	0.01±0.01	-0.01; 0.04	0.347	-	-	-
CRP	-0.06±0.04	-0.14; 0.12	0.096	-	-	-
log(PWV)	-0.39±0.09	-0.57; -0.20	<0.001	-0.17±0.04	-0.33; 0.01	<0.001
				Adjusted R2= 0.436; p<0.001		
log(PWV)						
Age	0.04±0.02	0.01; 0.07	0.049	-	-	-
Male gender	0.05±0.04	-0.28; 0.13	0.203	-	-	-
IPF presence	0.17±0.03	0.10; 0.23	<0.001	0.16±0.03	0.10; 0.23	<0.001
Leukocyte	0.02±0.01	0.01; 0.03	0.034	-	-	-
HDL	-0.03±0.01	-0.06; -0.01	0.013	-0.03±0.01	-0.05; -0.01	0.018
CRP	0.08±0.04	0.02; 0.16	0.016	0.11±0.04	0.04; 0.18	0.023
				Adjusted R2= 0.397; p<0.001		

Comorbidites and antifibrotics treatment effects were adjusted in all analyses.
Abbreviations: IPF: Idiopathic pulmonary fibrosis, HDL: High-density lipoprotein, PWV: Pulse wave velocity, FMD: Flow-mediated dilation, CIMT: Carotid-intima media thickness, β: Regression coefficient, SE: Standart error, CI: Confidence interval

Previous studies have shown the relationship between the PWV and coronary atherosclerosis (27, 28). The degree of atherosclerotic changes in the arterial system is significantly correlated with the PWV, and increased PWV, as a reflection of arterial stiffness, is an indicator of atherosclerosis. In addition, there is a positive correlation between PWV and endothelial dysfunction (24). To the best of our knowledge, we could not find any study evaluating arterial stiffness in IPF patients. However, it has been reported that the arterial stiffness increases in patients with chronic lung disease (29). In the current study, the PWV values were found to be higher in the IPF patients when compared to those in the control group. In addition, increased PWV values were found to be an independent predictor associated with decreasing FMD values and increasing CIMT values. In light of these findings, it was determined that increased arterial stiffness was associated with impaired endothelial function in patients with IPF and can contribute to the atherosclerosis process. Therefore, determining endothelial dysfunction in terms of both atherosclerotic process and cardiovascular risk may be important for prognosis in patients with IPF.

The main limitation of this study was that it did not allow for the establishment of the cause-effect relationship between IPF and atherosclerosis as a result of its cross-sectional nature. There may be a tight link between IPF and endothelial dysfunction; however, contrary to studies that have shown that IPF causes endothelial damage, it has also been shown that endothelial microparticles (30), and microvascular endothelial cell damage, and antiendothelial cell antibodies may play a role in the pathogenesis of IPF (31). Therefore, prospective controlled studies are needed on larger populations. Other important limitations included the low number of patients, as this was a single-center study, not evaluating atherosclerosis with coronary angiography, and not measuring the biochemical markers of the endothelial functions, such as asymmetric dimethyl arginine.

CONCLUSION

IPF patients without traditional or additional cardiovascular risk factors have elevated risk of endothelial dysfunction and atherosclerosis. A sustained inflammatory response may have play an important role in the process of atherosclerosis. Evaluating CIMT and FMD for subclinical atherosclerosis is technically difficult, requires highly skilled operators, and is expensive, and difficult to use as a readily available screening tool. Therefore, both endothelial dysfunction and subclinical atherosclerosis can be easily detected with PWV in patients with IPF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Training and Research Hospital Ethics Committee (Date: 13.09.2019, Decision No: 1985).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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